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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,894	12/15/1999	MARC PIECHACZYK	19141-007	5731

7590 04/10/2007

PATENT ADMINISTRATOR
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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/341,894	PIECHACZYK ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,53,55,60 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,53,55,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 1/22/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 52-53, 55, 60-61 are pending. Claims 1-51, 54, 56-59 are canceled.

Claims 52-53, 55, 60-61 are under consideration.

Specification

The objection to the title of the invention is not descriptive is withdrawn.

Claim Objections

Claims 52 and 57 objection because of minor informalities is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-53, 55, 60-61 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the office action mailed 8/24/06. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotype response directed against said antibody in

said mammal by transplanting a genetically modified mammal cell which comprises a polynucleotide sequence encoding said antibody or fragment thereof to be delivered, a promoter controlling expression of the nucleotide sequence and an element guaranteeing the secretion of the encoded antibody or fragment thereof, wherein said polynucleotide is expressed and the cell secretes the encoded antibody or fragment thereof such that the antibody or fragment thereof reaches the blood circulation of the subject mammal, and wherein said cell is a cell not specialized for the production of antibodies and which has the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from the subject mammal or from another mammal, which is a compatible donor, or is made compatible for an organ transplant.

The present specification fails to provide any guidance for overcoming the natural response to a mammal to a foreign antigen in this case an anti-idiotypic response against a recombinant antibody produced at an ectopic site in vivo. Applicants disclose the quantity of anti-idiotype antibody was determined by ELISA. As discussed in the previous office action in view of the art of record, there is no inherent property of the general delivery method that would prevent the immune system of a mammal to react to a new foreign antigen, and more specifically one that would prevent antibodies displaying an anti-idiotype property. Applicants have not performed in vivo experiments of the produced recombinant antibody at the ectopic site to detect levels of an anti-idiotypic response that are not detected by the sensitivity of the ELISA assay in vitro. New limitations requiring the non-antibody producing cell to have the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from another mammal, which is a compatible donor, or is made compatible for an organ transplant are not supported by the specification. The art of allogeneic or xenogeneic cell antibody-mediated gene/cell therapy is an unpredictable art with respect to the survival of non-antibody producing cells at the ectopic site in vivo, levels of recombinant antibody and proteins

produced after transplantation, in vivo. **Qu et al,** (The Journal of Cell Biology, 142: 1257-1267, 1998) at the time of the instant invention reports the application of cell and gene therapy in combination is facing major hurdles (p 1258, 2nd column, last paragraph). Qu reports through the combination of myoblast transplantation and gene therapy, the ex vivo gene transfer approach has been investigated as a gene delivery approach in the skeletal muscle and both the ex vivo procedure and the myoblast transfer approach are limited by the poor survival of the injected myoblasts (p 1258, 2nd column). Qu also reports the origin of the myogenic cells may influence their survival (abstract). Applicants also report the grafting of epidermis reconstituted in vitro on dermal substrates to SCID mice and antibody production was detectable in the blood for approximately one month and declined after 45 days (**Noel et al,** The Journal of Investigative Dermatology, 118: 288-294, 2002) (p 291-292), however, there is no indication of an antibody reaching the blood circulation in a quantity which is therapeutically effective. Note, even after the filing of the instant application, Applicants in this article (**Noel et al,** The Journal of Investigative Dermatology, 118: 288-294, 2002) report the application of cutaneous gene transfer to humans as well as to animal preclinical models has lagged far behind that of visceral tissues because of the existence of natural cutaneous barrier mechanisms resisting the insertion and/or stable expression of foreign genetic material and consistent with this serum antibody concentrations were modest and duration of antibody production was relatively limited in time and lack of high titer antibody-producing vectors, whatever their nature, most probably constitutes a major hurdle to efficient long-term skin-based genetic immunotherapies (p 293, 1st and 2nd column). In view of the art and the teachings in the specification to the filing date of the instant application, the issues regarding the unpredictability of antibody-mediated gene/cell therapy remain the same and have not be resolved by the guidance provided by the instant specification.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for antibody-mediated gene/cell therapy, wherein a cell derives from an allogeneic or xenogeneic mammal which is a compatible donor, particularly is made compatible for an organ transplantation, the lack of direction or guidance provided by the specification for antibody-mediated gene/cell therapy, the absence of working examples that correlate to the treatment of a disease by antibody-mediated gene/cell therapy, the unpredictable state of the art with respect to antibody-mediated gene/cell therapy, the undeveloped state of the art pertaining to the treatment of a disease by antibody-mediated gene/cell therapy, and the breadth of the claims directed to all diseases and cell types, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue the present invention comes from the observation that, in a subject mammal transplanted with non-B cells derived from the subject mammal **or** from another compatible donor mammal that have been genetically modified to produce and secrete antibodies, the produced antibodies show biophysical binding properties (Kon and Koff and K_A and K_D) comparable to those of antibodies naturally produced by cells of the B lineage. These arguments are not persuasive.

Applicants have shown the binding properties studies of the antibody produced by the genetically modified cells is comparable to antibodies naturally produced. However, for the reasons set forth in Qu et al, and Noel et al, expression of antibodies with the proper physical characteristics does not predict successful treatment as claimed. The record does not set forth evidence that overcomes the art recognized unpredictable nature of the invention. The method does not provide a means for enablement. Especially given the claims encompass xenotransplantation. Further, it is noted, Applicants have not provided evidence of detection of an anti-idiotypic response in vivo under conditions that are not detectable by the sensitivity

measurements of the ELISA assay or the antibody binding studies in vitro. Thus, the absence of detection could reflect the limitations of the assay not the lack of active antibodies.

Applicants argue from the experimental work presented in the present application, one could not state that no adverse anti-idiotypic response would be elicited against antibodies produced by genetically modified non-B cells because of post-translational modifications such as glycosylations between antibodies naturally produced by B cells and recombinant antibodies produced by genetically modified non-B cells. Moreover recombinant antibodies produced in vivo in a tissue environment such as the muscle, skin or liver, which differs from the natural environment of antibody-secreting plasmatocytes it could not be excluded that this new environment due to its particular composition would play an adjuvant role favoring the induction of an anti-idiotypic response against the recombinant antibodies. Applicants argue to further support the absence of adverse anti-idiotypic responses against recombinant antibodies produced in vivo by non-antibody producing cells, the Applicants provide a post-filing publication by Noel and Piechazyk which shows that in immunocompetent mouse transplanted with mouse fibroblasts expressing antibodies, no anti-idiotypic response against an ectopic antibody produced in a mammal upon genetic modification of cells that do not naturally produce antibodies.

Applicants support the notion that there could be an anti-idiotypic antibody response against a recombinant antibody produced in vivo at an ectopic site. This is confusing as the claims state without triggering such a response. Thus, the method could very well trigger such a response rendering the claim not enabled. Evidence an/or arguments regarding an anti-idiotypic response are needed.

Applicants in the provided publication report that one of the major limitations of repeated moAb infusion is the possible development of neutralizing anti-idiotypic responses by the

treated individuals, this criteria has to be met for testing whether skin fibroblasts-mediated delivery of moAb can stimulate an anti-idiotypic response in immunocompetent grafted mice (p 3, 1st column). Applicants in the same publication report that the short half life of any decrease in the production of recombinant Tg10 production in vivo is due to gene expression shut of or alteration of grafts (p 3, 1st column, last paragraph). Applicants conclude that the recombinant antibody production they observed by the mouse skin fibroblast in vivo whether this conclusion can be extrapolated to humans requires further investigation and a possible limitation to gene/cell therapies aiming at the systemic delivery of exogenous proteins is the mounting of a treatment-neutralizing immune response. As such Applicants fail to address any issue regarding an immune response and antibody. In view of the record there is no inherent property of the genera delivery method that would prevent the immune system of a mammal to react to a new foreign antigen and more specifically one that would prevent antibodies displaying an anti-idiotypic property.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 52 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 recites the method is practiced "without triggering an anti-idiotype response directed against said antibody in said mammal" however, there are no method steps to how this is accomplished. The claimed method is incomplete lacking essential method steps to how one would prevent triggering a response in a mammal to a foreign antigen in this case an anti-idiotype response to a foreign antibody in a mammal.

Claim 61 is vague and incomplete in the recitation of "therapeutically effective" because what therapy is encompassed or to be affected by the general method of delivery set forth in claim 52 is not clearly set forth. If it is a "therapeutic antibody" being produced (as generally taught in the specification, paragraph 16), there is insufficient antecedent basis for this in claim 52.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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